Abacavir/Lamivudine

Brand Name: Epzicom
Drug Class: Nucleoside Reverse Transcriptase Inhibitors

Drug Description

Abacavir sulfate/lamivudine (Epzicom) is a fixed-dose tablet containing two nucleoside reverse transcriptase inhibitors (NRTIs): abacavir sulfate and lamivudine. Each tablet contains 600 mg of abacavir sulfate and 300 mg of lamivudine. [1]

HIV/AIDS-Related Uses

Epzicom was approved by the FDA on August 2, 2004, for combined use with other antiretroviral agents in the treatment of HIV-1 infection. When used as part of a three-drug HIV treatment regimen, Epzicom should be used with antiretroviral agents from different pharmacological classes, and not with other NRTIs.[2] [3]

Pharmacology

Both of the nucleoside analogues contained in Epzicom inhibit HIV reverse transcriptase (RT), an enzyme essential for HIV replication. Abacavir, a carbocyclic synthetic nucleoside analogue, is phosphorylated intracellularly to the active metabolite carbovir triphosphate, an analogue of deoxyguanosine-5'-triphophate (dGTP). Carbovir triphosphate inhibits the activity of HIV-1 RT by competing with dGTP for incorporation into viral DNA, resulting in termination of the DNA chain. Lamivudine, also a synthetic nucleoside analogue, is phosphorylated intracellularly to the active metabolite lamivudine triphosphate (L-TP), which inhibits HIV DNA synthesis in a manner analogous to abacavir.[4]

Following oral administration, abacavir is rapidly absorbed and extensively distributed. After administration of a single oral dose of 600 mg of abacavir, the peak plasma concentration (Cmax) was 4.26 mcg/ml (SD 1.19) and the area under the plasma concentration-time curve (AUC) was 11.95 mcg hr/ml (SD 2.51). Binding to plasma proteins is approximately 50% and is independent of concentration. Abacavir distributes readily into erythrocytes. The primary routes of abacavir elimination are metabolism by alcohol dehydrogenase to form the 5'-carboxylic acid and glucuronyl transferase to form 5'-glucuronide.[5]

Following oral administration, lamivudine is also rapidly absorbed and extensively distributed. After multiple-dose oral administration of lamivudine 300 mg once daily for 7 days in healthy subjects, steady-state Cmax was 2.04 mcg/ml (SD 0.54) and the 24-hour steady-state AUC was 8.87 mcg x hr/ml (SD 1.83). Binding to plasma protein is low. Approximately 70% of an IV dose of lamivudine is recovered unchanged in urine; metabolism is a minor route of elimination.[6]

Results of a bioavailability study comparing administration of one Epzicom tablet to simultaneous administration of two 300 mg abacavir tablets and two 150 mg lamivudine tablets to healthy subjects showed no difference in absorption, as measured by AUC and Cmax.[7]

Epzicom is in FDA Pregnancy Category C. No adequate or well-controlled studies have been done in pregnant women. Studies in rats have shown that abacavir crosses the placenta. Fetal malformations and developmental toxicity occur in rats given a dose of abacavir equivalent to 35 times the recommended human exposure. In rabbits, no developmental toxicity or increased fetal malformations occurred at doses equivalent to 8.5 times the recommended human exposure. Studies of lamivudine in rats have shown that the drug crosses the placenta. No lamivudine-associated teratogenicity was observed in rats or in rabbits given doses equivalent to 35 times the recommended human exposure. Evidence of early embryolethality was seen in rabbits at exposure levels similar to the recommended human exposure; however, no embryolethality was observed in rats at exposure levels up to 35 times the recommended human dose. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to antiretroviral agents, including Epzicom.[8] Physicians may register patients by calling 1-800-258-4263 or online at http://www.APRegistry.com.[9]

Abacavir is secreted into the milk of lactating rats, and lamivudine is excreted into milk in rats and humans. Because of the potential for HIV transmission and for serious adverse drug effects in

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Pharmacology (cont.)

breastfed infants, women who are receiving Epzicom should be instructed not to breastfeed.[10]

HIV-1 isolates with reduced susceptibility to the combination of abacavir and lamivudine have been selected in vitro and have also been obtained from patients failing abacavir/lamivudine-containing regimens. Genotypic characterization of abacavir/lamivudine-resistant viruses selected in vitro identified the following amino acid substitutions in HIV-1 RT: M184V/I, K65R, L74V, and Y115F. In a study of treatment-naive adults receiving abacavir 600 mg once daily or 300 mg twice daily with a background regimen of both lamivudine 300 mg and efavirenz 600 mg once daily, the abacavir- and lamivudine-associated resistance mutation M184V/I was the most commonly observed.[11]

Cross resistance has been observed among NRTIs. Viruses containing abacavir and lamivudine resistance-associated mutations, namely K65R, L74V, M184V, and Y115F, exhibit cross resistance to didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine both in vitro and in patients. The K65R mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zalcitabine; the L74V mutation can confer resistance to abacavir, didanosine, and zalcitabine; and the M184V mutation can confer resistance to abacavir, didanosine, emtricitabine, lamivudine, and zalcitabine. Viruses with the K65R mutation (with or without the M184V/I mutation), the L74V plus M184V/I mutation, and the M184V/I mutation plus thymidine analogue mutations (TAMs) M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/N have demonstrated decreased susceptibility to Epzicom. An increasing number of TAMs is associated with a progressive reduction in abacavir susceptibility.[12]

Adverse Events/Toxicity

Epzicom contains abacavir sulfate, which has been associated with serious and sometimes fatal hypersensitivity reactions. In clinical studies, hypersensitivity to abacavir was reported in approximated 8% of patients. Symptoms usually appear within the first 6 weeks of treatment, but may occur at any time during therapy. Hypersensitivity to abacavir is a multiorgan syndrome usually characterized by at least two of the following manifestations: fever; rash; malaise, fatigue, or achiness; gastrointestinal symptoms of nausea, vomiting, diarrhea, or abdominal pain; or respiratory symptoms of dyspnea, cough, or pharyngitis. Less common signs and symptoms of hypersensitivity include lethargy, myolysis, edema, abnormal chest x-ray, and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, and death have occurred in association with hypersensitivity reactions.[13] In one study, once-daily dosing of abacavir was associated with more severe hypersensitivity reactions.[14] Physical findings associated with abacavir hypersensitivity include lymphadenopathy, mucous membrane lesions, and rash that is usually maculopapular or urticarial. There have also been reports of erythema multiforme with abacavir use.[15] Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir in combination with other medications associated with SJS and TEN. Because the clinical signs and symptoms of abacavir hypersensitivity overlap with those of SJS and TEN, and because some patients may have multiple drug sensitivities, patients with suspected SJS or TEN should discontinue Epzicom treatment.[16] Laboratory abnormalities associated with abacavir hypersensitivity include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, and lymphopenia.[17] An Abacavir Hypersensitivity Registry has been established to facilitate reporting of hypersensitivity reactions. Physicians should register patients by calling 1-800-270-0425.[18]

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues (alone or in combination), including abacavir, lamivudine, and others. Female gender, obesity, and prolonged nucleoside analogue exposure may be risk factors. Caution should be exercised in any patient with known risk factors for liver disease; however, liver problems have been reported in patients with no known risk factors. Treatment with Epzicom should

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Adverse Events/Toxicity (cont.)

be suspended in any patient who develops clinical or laboratory findings that suggest lactic acidosis or pronounced hepatotoxicity.[19] Exacerbation of hepatitis has occurred in patients treated for chronic hepatitis B infection after discontinuation of lamivudine therapy.[20]

Immune reconstitution syndrome has been reported with the use of combination anti-HIV therapy, including abacavir/lamivudine. Patients who develop immune system responses to anti-HIV therapy may develop an inflammatory response to residual opportunistic infections (e.g., Mycobacterium avium infection; cytomegalovirus; Pneumocystis jirovecii pneumonia; tuberculosis).[21]

Other reported adverse effects of abacavir and lamivudine include redistribution of body fat; stomatitis; hyperglycemia; generalized weakness; aplastic anemia; other anemias; lymphadenopathy; splenomegaly; pancreatitis; muscle weakness; rhabdomyolysis; paresthesia; peripheral neuropathy; seizures; abnormal breath sounds and wheezing; and alopecia.[22]

Drug and Food Interactions

Epzicom may be administered with or without food. Administration of Epzicom with a high-fat meal did not change the bioavailability of lamivudine. Food did not alter the extent of systemic exposure to abacavir, but the rate of absorption decreased approximately 24% compared to fasted conditions.[23]

Abacavir and lamivudine are not significantly metabolized by the cytochrome P450 enzymes, nor do they inhibit or induce this enzyme system; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways.[24] Abacavir administered at twice the recommended dose increased methadone clearance by 22%. A small number of patients receiving both Epzicom and methadone may need a methadone dosage adjustment. Consumption of alcohol may cause an increase in abacavir exposure. Lamivudine AUC was increased by 43% when coadministered with sulfamethoxazole/trimethoprim. Concurrent administration of lamivudine and nelfinavir resulted in a 10% increase in lamivudine AUC.[25]

Results of in vitro studies indicate that ribavirin reduces the phosphorylation of pyrimidine nucleoside analogues, including lamivudine. Liver decompensation has occurred in patients coinfected with HIV and hepatitis C virus (HCV) receiving combination anti-HIV therapy for HIV and interferon alpha with or without ribavirin.[26]

Epzicom contains fixed doses of abacavir and lamivudine and should not be administered concomitantly with other abacavir-containing and/or lamivudine-containing products.[27]

Contraindications

Epzicom is contraindicated in patients with previously demonstrated hypersensitivity to abacavir or to any other component of the product. Following a hypersensitivity reaction to abacavir, patients should never restart Epzicom or any other abacavir-containing product. Fatal reactions have been associated with readministration of abacavir to patients with a history of abacavir hypersensitivity. Epzicom is also contraindicated in patients with hepatic impairment and in patients with creatinine clearance less than 50 ml/min.[28]

Clinical Trials

For information on clinical trials that involve Abacavir/Lamivudine, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Abacavir/Lamivudine AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[29]

Dosage Form: Film-coated tablet containing abacavir sulfate 600 mg and lamivudine 300 mg.

Because it is a fixed-dose tablet, Epzicom should not be prescribed for patients requiring dosage adjustment.[30]

Storage: Store at 25 C (77 F); excursions permitted

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Dosing Information (cont.)

to 15 C to 30 C (59 F to 86 F).[31]

Chemistry

CAS Name: Abacavir sulfate: (1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate[32]

Lamivudine: 2(1H)-Pyrimidinone, 4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-,(2R-cis)[33]

CAS Number: Abacavir sulfate: 188062-50-2[34]

Lamivudine: 134678-17-4[35]

Molecular formula: Abacavir sulfate: 2(C14-H18-N6-O)(H2-O4-S) / Lamivudine: C8-H11-N3-O3-S[36]

Abacavir sulfate: C50.1%, H5.7%, N25.1%, O14.3%, S4.8% / Lamivudine: C41.91%, H4.84%, N18.33%, O20.94%, S13.99%[37]

Molecular weight: Abacavir sulfate: 670.76 / Lamivudine: 229.26[38]

Physical Description: Abacavir sulfate: white to off-white solid.[39]

Lamivudine: white to off-white crystalline solid.[40]

Solubility: Abacavir sulfate has a solubility of approximately 77 mg/ml in distilled water at 25 C.[41]

Lamivudine has a solubility of approximately 70 mg/ml in water at 20 C.[42]

Other Names

Abacavir sulfate/Lamivudine[43]

Further Reading

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Manufacturer Information

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Research Triangle Park, NC 27709
(888) 825-5249

Epzicom
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Abacavir/Lamivudine

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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